The Science and Engineering of Bone Cements and Bone Substitution Biomaterials: A State-of-the-Art Review

Η Επιστήμη και η Τεχνολογία των Οστικών Τσιμέντων και των Βιοϋλικών για Οστική Αποκατάσταση: Βιβλιογραφική Ανασκόπηση

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Abstract

The first bone biomaterials for biomedical applications were discovered in the 1920s. Nine decades later, the interest for these materials is still rising. The goal of the present paper is to review the most recent achievements in the field of bone cements and bone substitution biomaterials and to analyze future directions in research and development. A classification of the related materials in 4 groups has been introduced and a set of fundamental design criteria that should be considered prior to the development of such materials is presented.

Περίληψη

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Τα πρώτα βιοϋλικά για την αποκατάσταση οστικών ανακαλύφθηκαν γύρω στο 1920. Εννέα δεκαετίες αργότερα, το ενδιαφέρον για αυτή την κατηγορία υλικών συνεχώς αυξάνει. Στόχος του παρόντος άρθρου είναι η ανασκόπηση των τελευταίων εξελίξεων στον τομέα των οστικών τσιμέντων και των συναφών βιοϋλικών οστικής αποκατάστασης και η ανάλυση των μελλοντικών τάσεων - κατευθύνσεων στην έρευνα που διεξάγεται διεθνώς σχετικά με τα παραπάνω υλικά, τα οποία και ταξινομήθηκαν σε 4 κατηγορίες. Επιπρόσθετα παρουσιάζεται και μια σειρά από βασικά κριτήρια σχεδιασμού που θα πρέπει να ικανοποιούν τα εν λόγω υλικά κατά την σύνθεσή τους τόσο σε εργαστηριακή όσο και σε βιομηχανική κλίμακα.

Keywords: Bone Cement, Bone Substitution Materials, Acrylic Bone Cements, Calcium Phosphate Cement, Hydroxyapatite, Vertebroplasty, Kyphoplasty.

1. Introduction

Human bone is an impressive tissue since it provides our physical support, protection and the means for locomotion. Despite being 50-60 vol.-% ceramic hydroxyapatite (HA) [1], it combines high strength with toughness and can often repair itself without surgical intervention. However, trauma, disease, and congenital deformity can require the use of a graft to fill space to prevent fibrous tissue in growth during healing, restore cosmetic appearance, and to act as a scaffold for new bone formation. The use of synthetic materials offers the advantage of a potentially more reproducible graft that can be processed into different forms such as porous blocks, carvable composites, controlled morphology granules, cements, etc.

The current generation of biomaterials for biomedical applications is being designed to be bioactive and resorbable. Once implanted, they are intended to, for example, activate gene expression, stimulate specific cellular responses at the molecular level, and help the body heal itself. The emphasis is no longer on merely replacement tissue [2]. Current advances in molecular biomimesis suggest that a biomineral-inspired approach may be of value in new classes of biomaterials [3]. This approach is based, primarily, on the idea of macromolecules as templates to control inorganic crystal formation, and seeks to reproduce the nanoscopic and hierarchical structures of natural bone through biological principles and the processes of self-assembly or self-organization [4]. Recently, macromolecules, as controllers of mineral nucleation and growth for the synthesis of mineral–polymer composite biomaterials, have generated considerable interest [5–8].

2. Bone cements

Bone cements are well suited to their function and have an excellent performance record. Despite several modifications, proposed as alternatives to the original formulations, none have been successfully introduced in the market. Therefore, injectable bone cements are still the gold standard in arthroplasty. This does not mean bone cements are free of drawbacks that limit their performance. On the contrary, problems such as thermal or chemical necrosis of the bone, high porosity, low interfacial strength between cement and bone and between cement and prosthesis, residual shrinkage stresses, infection and inflammation, among other complications, may occur [9], ultimately leading to aseptic loosening of the implant, the major cause of failure of hip arthroplasties [9, 10]. Therefore, the search for modified formulations with improved mechanical and biological properties and better overall performance has been keen in recent years [11].

The alterations to the conventional formulation have included fiber reinforcement (which was intended to improve mechanical properties, but presented serious drawbacks regarding handling), addition of bioactive fillers (which simultaneously improve mechanical properties and allow direct bonding to bone), replacement of radiopaque agents, toughened cements (by the addition of rubber particles or hydrophilic moieties), development of novel activators, partially degradable formulations (developed to improve the drug release profile of the cements, at the cost of compromised mechanical properties), crosslinked cements (developed to decrease chain mobility and improve mechanical properties) and two-solution formulations (as opposed to formulations with one solid and one liquid component). Accordingly, there are several review papers dealing with both the performance of commercially available cements and the properties of novel formulations [12].

3. Desirable properties of bone cements

The list of desirable properties for injectable bone cements, as identified by different workers, is a long one [13]. However, a consensus appears to be that the most important of

these properties are easy injectability, high radiopacity, a setting dough viscosity that does not change much between mixing and delivery into the vertebral body, a resorption rate that is neither too fast nor too slow, and mechanical properties that are comparable to those of a healthy intact vertebral body [14].

4. Classification of bone cements

Bone cements may be classified into 4 classes; namely, acrylic bone cements, calcium phosphates, calcium sulfates and composites. The main features and several commercially available brands of injectable bone cements are listed in Table 1.

Table 1. Examples of commercially available Bone Cements for Vertebroplasty and/or Kyphoplasty

Class	Composition[1]	Manufacturer/Supplier
	Acrylic Bone Cements [2]	
CMW™3	10 wt/wt % $BaSO_4$ + 1 g W powder	CMW-DePuy, Blackpool, UK
Codman Cranioplastic®	5-6 g $BaSO_4$ + 1 g W powder	CMW-DePuy, Blackpool, UK
KyphX® HV-R™	Contains 30 wt/wt % $BaSO_4$; approved by the US Food and Drug Administration (FDA) for use in KP	Kyphon, Inc., Sunnyvale, CA
Osteopal® V	33 wt/wt % ZrO_2	Heraeus Kulzer GmbH, Wehrheim, Germany
Palacos® E	15 wt/wt % ZrO_2 + 10 ml of dye	Heraeus Kulzer GmbH, Wehrheim, Germany
Surgical Simplex® P	20 wt % $BaSO_4$ + 1-2 g Ta powder	Stryker-Howmedica-Osteonics
Symphony™ VR Radiopaque	Approved by the FDA for use in VP or KP	Advanced Biomaterial Systems, Inc., Chatham, NJ
	Calcium Phosphates	
α-BSM (Bone Substitute Material) [Biobon®]	Amorphous CaP + DCPD	ETEX, Cambridge, MA
Biopex R®	75% *α*-TCP + 18% TTCP + 5% DCPD + 2% HA	Mutsubishi Materials Co., Saitama, Japan
BoneSave®	80 wt % TCP + 20 wt % HA	Stryker-Howmedica-Osteonics, Mahwah, NJ
BoneSource® BVF	TTCP, DCP	Stryker-Howmedica-Osteonics, Mahwah, NJ
ChronOS Inject™	42 wt. % *β*-TCP + 21 wt. % MCPM + 3 wt. % *β*-TCP granules + 5 wt. % magnesium hydrogen phosphate + <1 wt. % sodium hydrogen pyrophosphate and $MgSO_4$	Synthes, Inc., West Chester, PA
Calcibon®	*α*-TCP + $CaHPO_4$ + $CaCO_3$ + precipitated HA	Biomet Europe, Dordrecht, The Netherlands
Eurobone®	TCP	F-H Orthopedics, Heimsbrum, France
Norian®SRS®	*α*-TCP, $CaCO_3$, MCPM	Synthes
	Calcium Sulfates	
BonePlast™	$CaSO_4$ 0.5 H_2O powder	Interpore Cross International,

MIIG® X3	$CaSO_4$ 0.5 H_2O powder	Inc., Irvine, CA Wright Medical Technology, Inc., Arlington, TN
	Composites	
Cortoss®	*bis*-GMA/*bis* -EMA/TEGDMA monomer matrix (59 vol %) reinforced with glass ceramic particles, whose surfaces are treated with 3MPS (41 vol %); initiator: BPO; activator/coinitiator: DHEPT; stabilizer: BHT	Orthovita, Inc., Malvern, PA

[1] CaP, calcium phosphate; DCPD, dicalcium phosphate dihydrate; TCP, tricalcium phosphate; TTCP, tetracalcium phosphate; HA, hydroxyapatite; DCP, dicalcium phosphate; MCPM, monocalcium phosphate monohydrate; *bis*-GMA, 2,2-*bis* [4-(2-hydroxymethacryloxypropyl)phenyl] propane; *bis*-EMA, 2,2-*bis* [4-(2-methacryloxyethoxy)] phenyl propane; TEGDMA, triethylene glycol dimethacrylate; 3MPS, 3-methylacryloxy-propyltrimethoxysilane; BPO, benzoyl peroxide; DHEPT: di(hydroxy-ethyl)-*p*-toluidine; BHT: 2,6-di-*tert*-butyl-*p*-cresol.
[2] For the acrylic bone cement brands, typical radiopacifiers and their loadings, when used in Vertebroplasty (VP) and Kyphoplasty (KP), are indicated. Details on other constituents of the cements are to be found in the product brochures.

4.1. Acrylic bone cements

Acrylic bone cements, mainly consisting of polymethylmethacrylate (PMMA), have been used in dentistry and orthopedic surgery for prosthetic fixation for more than forty years [15] since it was introduced by Charnley [16]. Nevertheless, PMMA cement possesses several inherent problems, such as non bone bonding capability, thickening of the intervening fibrous tissue layer that leads to aseptic loosening of the cement in some cases [17], relatively low mechanical strength [18] which can result in cement fracture and the production of wear debris due to abrasion that can lead to prosthetic loosening [19] and high heat generation during polymerization [20].

To overcome mechanical weakness, bone cements are usually reinforced with additives, such as carbon, graphite, aramid, bone particles, polyethylene, titanium, ultra-high molecular weight polyethylene, PMMA fibers, tricalcium phosphate, and hydroxyapatite [21]. Hence, bioactive bone cements (BABCs) have been developed that combine CaO-SiO_2-P_2O_5-CaF_2 glass, MgO-$CaOSiO_2$-P_2O_5-CaF_2 glass or MgO-CaO-SiO_2-P_2O_5-CaF_2 apatite and wollastonite containing glass ceramic (AW-GC) powder with a bisphenol-A-glycidyl dimethacrylate (*bis*-GMA) based resin [22–24]. These cements show direct contact with living bone through a “Ca-P rich layer.” They also demonstrate the ability to bond to bone under load-bearing and non-load-bearing conditions [25–28]. To achieve higher mechanical strength and better handling properties (e.g., increased viscosity), silica glass powder was added to the BABC as a second filler [29]. A silica powder content of up to 25% (w/w) did not strongly inhibit the bioactivity. Further, Kobayashi et al. [29], demonstrated that introducing a polymerization reaction inhibitor (phenothiazine), together with an increased amount of accelerator (*N,N*dimethyl-*p*-toluidine), improved the mechanical properties of BABC. It also made the uncured surface layer thinner and had no adverse effect on the osteoconductivity.

4.2. Calcium phosphate cements

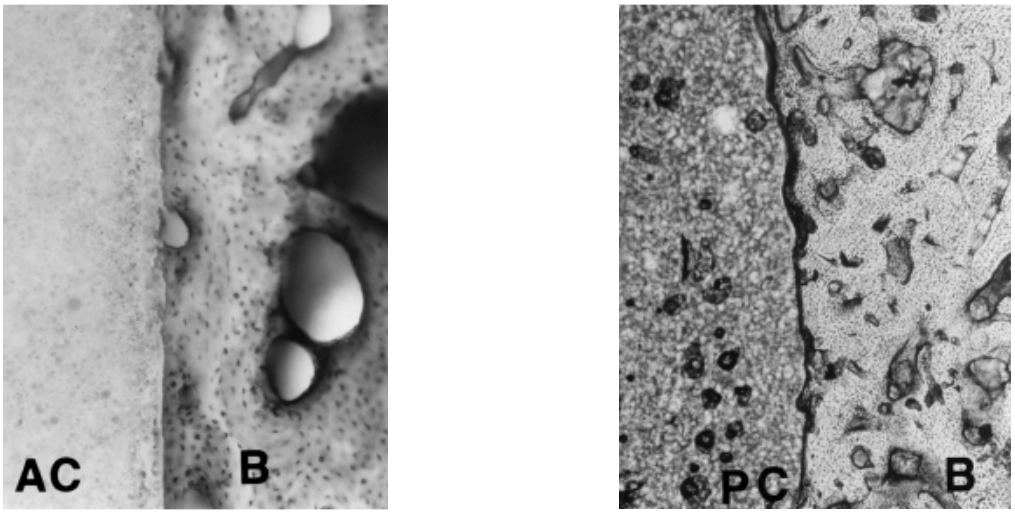
Calcium phosphate cements (CPCs) show several advantages with respect to other materials which are used for bone repair. For example, they are injectable, easy to shape and can be maintained locally. Therefore, they are very effective to fill bone defects with an irregular shape. Furthermore, CPCs are very bone compatible and osteoconductive (Figure 1). On the other hand, they have poor mechanical properties. Currently, this prevents their use in loaded conditions. This last problem is even enhanced by the fact that the *in vivo* resorption of CPC is very slow. In view of this, two types of resorption can be distinguished, i.e., passive and active.

Passive resorption is due to the dissolution rate of the material into the body fluids and it depends on the final components of the set cement. Further, this type of resorption is determined by the porosity of the samples, ionic substitutions, crystallinity and pH of the cement–tissue interface [30]. Active resorption is due to cellular activity (like osteoclast-like cells) and is, in this way, related with the passive one. The osteoclastic cells produce a pH close to 5.5, which in turn increases the dissolution rate of the implant. Usually this type of resorption only occurs on the cement surface because the pores as present in the cements do not allow the penetration of cells or blood vessels in the material [31–33].

Already several attempts have been made to improve the resorption behaviour of CPCs e.g. by increasing the porosity of the material. This can be achieved by using the so-called calcium phosphate emulsion technique [34, 35]. So far, the most extensive experiments have been done by mixing the CPC with crystals of the right dimensions of highly soluble and non-toxic compounds, such as sucrose [36] or mannitol [37]. After the complete hardening of the material the macrocrystals are removed just by soaking the samples in water. Although both methods have their merits, the disadvantage is that the porosity cannot be created during setting of the cement in the *in vivo* environment. For the emulsion technique, an additional heat treatment is required to achieve porosity. Addition of sucrose or mannitol requires dissolution of these components after application and setting of the cement in the bone defect in order to get macroporosity.

Recent studies focus interest on synthetic hydroxyapatite (HA), bovine hydroxyapatite (BHA), and β-tricalcium phosphate (β-TCP) as additives. Hydroxyapatite (HA) is the principal mineral of bone and teeth, with a chemical formula of $Ca_{10}(PO_4)_6(OH)_2$. Hydroxyapatite can be derived from natural sources, such as bovine bones, or corals via hydrothermal transformation, or it can be synthetically prepared [38, 39]. Highly pure synthetic HA can be prepared by solid-state reaction, by hydrothermal or microwave methods, or by sintering of apatite obtained via sol-gel method. Apatites derived from bovine bone (BHA) are obtained by chemical and/ or thermal removal of the organic matter whether without sintering or with sintering at temperatures above 1000°C. Pure tricalcium phosphate, *β*-TCP ($Ca_3(PO_4)_2$), is prepared either by solid-state reaction or by sintering of calcium-deficient apatite obtained from solutions [39]. To achieve mechanically strong cement composites, the silane treatment of the inorganic filler of the cements is a well-known and widely accepted approach in the technology of such composites. The goal of silane treatment is that it results in formation of strong bonds between the inorganic filler and the organic matrix [40].

The fluoridated HA [fluor-hydroxyapatite; FHA ($Ca_{10}(PO_4)_6(OH)_{2-2x}F_{2x}$)/fluorapatite; FA, ($Ca_{10}(PO_4)_6F_2$)] has also gained much attention in the area of dental restoration [41–43]. The existence of a large amount of fluorine on the outer layer of the teeth enamel is known to protect the teeth from dental caries and to stimulate the crystallization and mineralization of the bones [41, 42]. As such, the partial incorporation of fluorine, in order to elicit its biological functions, is one of the main themes in dental restoration research. However, the fluorine related research so far has mostly been focused on the ionic effects produced by adding sodium fluoride within a cell culture medium. Recently, attempts to incorporate fluorine in biomaterials have increased significantly. In most cases, fluorine was incorporated within glass and glass cement systems, in which fluorine ions were released in a controlled manner, so as to optimize their antibacterial effects. With regard to the fluoridated apatites, their fabrication method and physiochemical properties have previously been examined [44–48]. However, there have been few reports on the biological performance of FHA and FA either *in vitro* or *in vivo*. Prior to the utilization of the fluoridated apatites as hard tissue replacements, their biological efficacy needs to be addressed.



(a) (b)

Figure 1. Giemsa surface staining showing (a) an interface between bioactive bone cement cement (AC) and bone (B) in the acetabulum at 6 months. Direct contact between AC and B is demonstrated (x100) and (b) an interface between PMMA cement (PC) and bone (B) in the acetabulum at 6 months. There is an intervening connective tissue layer between PC and B (x20) [20].

4.3 Calcium Sulfate Cements

In its form known as plaster of Paris or gypsum, $CaSO_4$ has a long clinical history for use as a bone graft substitute in various skeletal sites, the use having been first proposed by Dreesmann in 1892 [49] and developed by Peltier in 1961 [50]. However, in the original form, the recrystallization of plaster of Paris after it is mixed with water is random, and the crystalline structure contains many defects. More recently, surgical-grade calcium sulfate cements (CSCs) have been developed, with the powder constituent being calcium sulfate hemihydrate [51]. When mixed with a diluent, the powder is converted to calcium sulfate dihydrate, producing a paste or putty with a solid or partially solid structure [51].

When used as an injectable bone cement, surgical-grade CSC inhibits fibrous tissue in growth, creates a slightly acidic environment that encourages angiogenesis and osteogenesis and, as the cement dissolves, bone forms, thereby allowing the void occupied by the cement to be replaced by new bone [52]. Depending on the volume and location, surgical-grade CSC filler resorbs, *in vivo,* mainly by dissolution, generally within about 2 months [53].

4.4. Composite Cements (CICs)

Cortical bone at the ultrastructural level is a HA-reinforced composite [54]. Therefore, the development of a cement analogous to the natural tissue requires materials with equivalent microstructural and deformational characteristics. Thus, the use of reinforced polymers simultaneously with a bioactive second phase material (e.g. ceramic, glass, etc.) offers the low elastic modulus associated with the polymer and high strength as a result of the chosen filler. Additional merit related to the use of composite materials is that by controlling the volume fractions and arrangement of the reinforcing phase, the properties and

design of an implant can be varied and tailored to suit the mechanical and physiological conditions of the host tissue. Achieving a stable implant-tissue interface during physiological loading, in contrast to that obtained with current orthopaedic implants, is top of the agenda.

Previous studies have shown that bioactive glass and glass-ceramics can bond chemically with host bone [55]. Their primary advantage is the ability to produce fast tissue bonding via a rapid rate of surface reaction. However, their main disadvantage lies in the fact that they form an amorphous 2D glass network [56]. The inherent low strength, fracture toughness and short critical crack propagation length that they experience means that they are confined to applications in low loaded or compressively loaded devices [57]. Glasses are thus not suitable as load bearing implants because they are brittle.

5. Conclusions

The synthesis of new substituting materials mimicking natural bone, as bone substitute biomaterials and autograft and allograft bone replacements, still remains one of the most interesting objectives of the technological research. The future of bone cement research, in accordance with current trends in biomaterials, rests on multifunctional systems that are able to interact with body tissues. In this way, much better overall performance may be achieved as compared with inert systems such as the commercially available cements. As most bone cement research has concentrated on increasing the cement–bone interaction (bioactive cements), other important characteristics have been neglected: compatibility with body fluids, penetration of bone inside the cement mantle, better distribution of the load from the prosthesis to the bone. Only multifunctional cements may be able to address all these issues simultaneously. There remains a great need for controlled, prospective, randomized studies to provide reliable information regarding the use of these materials.

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